REMARKS

Upon entry of the foregoing amendment, claims 1-11, 13-18, and 19-33 are pending in this application. Claims 19-30 are withdrawn from consideration. Claims 12 and 31 are newly cancelled herein without prejudice or disclaimer of the cancelled subject matter. Applicants reserve the right to pursue any cancelled subject matter in one or more continuing or divisional applications. Claims 1, 9, 11, 15, and 18 are newly amended herein. Claims 32 and 33 are newly added. Claims 1-11, 13-18, 32 and 33 are under examination.

Support for the amendments to claim 1 is found, for example, as follows:

for "effective amount of a combination," Figures 4 and 5;

for "combination of a CD40 specific binding agent and a CD20 specific binding agent," page 5, lines 7-13; Figures 4 and 5;

for "binding agent" page 5, lines 22-29; page 20, line 21; page 21, line 12;

for "sufficient for therapeutically effective treatment," Figures 4 and 5;

and, elsewhere throughout the specification.

Support for the amendments to claim 9 ("binding agent") is found, for example, on page 5, lines 22-29; page 20, line 21; page 21, line 12; and, elsewhere throughout the specification.

Support for the amendments to claim 11 ("is the monoclonal antibody secreted by the hybridoma having ATCC® Accession No. PTA-110") is found, for example, on page 27, lines 16-36; page 45, lines 29-31; and, elsewhere throughout the specification. "S2C6" (SGN-14) is an anti-CD40 antibody disclosed in International Publication No. WO 00/75348 A1 [Siegall] and in U.S. Patent No. 6,843,989 B1 [Siegall], column 8, lines 45-67; column 9, lines 1-7; and, column 34, lines 10-19.

The Siegall patent discloses the S2C6 antibody is a monoclonal antibody secreted from hybridoma S2C6, which has ATCC® accession number PTA-110. The Siegall

International Publication (application) is CIP of U.S. Appl. No. 09/328,296 which is a priority application for the U.S. Siegall patent. A copy of the Siegall International Publication front page showing the relationship is enclosed herewith (Exhibit A) for the convenience of the Examiner. Both the Siegall International Publication and the Siegall U.S. patent are incorporated by reference in the instant application (see, for example, page 44, lines 23-25). Thus, the specification has support for the ATCC® accession No. PTA-110.

Support for the amendments to claims 15 and 18 ("the antibody produced by the transfectoma having ATCC® deposit No. 69119") (*i.e.*, the chimeric anti-CD20 antibody) is found, for example, on page 21, lines 15-17; and, elsewhere throughout the specification. The anti-CD20 antibody is identified in the instant specification (see, for example, page 17, lines 3-7; page 21, lines 15-17) as rituximab, which is identified as the "C2B8" antibody in U.S. Patent No. 5,736,137 [Anderson] (column 21, beginning at line 19).

The Anderson patent discloses the nucleotide sequence encoding the "C2B8" antibody (rituximab) is in TCAE 8 (a transformed *E. coli* for purposes of deposit) having ATCC® deposit number 69119 (anti-CD20 in TCAE 8) (column 32, lines 13-27). The Anderson patent is incorporated by reference in the instant application (see, for example, page 44, lines 23-25). Thus, the instant specification has support for the monoclonal antibody produced by the transfectoma having ATCC® deposit number 69119.

Support for new claims 32 and 33, is found, for example, on page 42, lines 15-17, and elsewhere throughout the specification.

The amendments to the claims are believed to put the application in condition for allowance, or alternatively, in better form for appeal. The amendment is not believed to add new matter. Thus, entry is appropriate and respectfully requested.

A. New Matter Rejection Under 35 U.S.C. § 112

The Examiner stated the recitation of "a CD40 agonist" and the purported new matter issues under 35 U.S.C. § 112, first paragraph, are outside the scope of the subject matter of U.S. Appl. No. 60/280,805. As a result, the Examiner concluded that the priority date of the instant claims is no longer based on U.S. Appl. No. 60/280,805, filed April 2, 2001. The argument is respectfully traversed.

Without acquiescing to the propriety of the argument, the term "agonist" has been deleted from claims 1 and 9. The amendments to claims 1 and 9 are believed to moot the argument. Applicants are entitled to the priority date of provisional application 60/280,805 filed April 2, 2001 and acknowledgement of such by the Office is respectfully requested.

B. Rejection of Claims 1-18 and 31 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-18 and 31 are rejected under 35 U.S.C. § 112, second paragraph, for purportedly being indefinite. The rejection is respectfully traversed. Claims 12 and 31 are newly cancelled and all rejections applied to claims 12 and 31 are therefore moot.

a) Claims 11, 15 and 18 are allegedly indefinite in the recitation of "rituximab" and "S2C6." The Office alleges that the designations "S2C6" and "rituximab" are mere laboratory designations which do not clearly define the claimed products because different laboratories may use the same designations to define completely distinct cell lines.

Without discussing the merits of the rejection, claims 11, 15 and 18 have been amended to now claim the anti-CD20 and anti-CD40 antibodies by ATCC® deposit numbers as suggested by the Examiner. Office Action at 3. In view of the amendments to the claims, and the suggestion by the Examiner that recitation of the appropriate ATCC® accession/deposit numbers would overcome the rejection, the rejection is believed to be overcome.

Claims reciting partial variable light and heavy domain sequences of the S2C6 antibody have been amended and, as amended, no longer recite the sequences.

b) At page 3 of the Office Action, the Office argues claims 15 and 18 contain the trademark or tradename "rituximab" and therefore the claim scope is allegedly uncertain because the trademark or tradename does not identify or describe goods associated with the trademark or tradename. Contrary to the Examiner's statement, "rituximab" is the generic name for the anti-CD20 antibody and is not the trademark name.

However, claims 15 and 18 have been amended to refer to the antibody by ATCC® deposit accession number and no longer recite the term "rituximab." RITUXAN® is the trademark name for rituximab. Applicants have reviewed the specification and the specification is believed to correctly designate trademarked products where appropriate.

c) The Office alleges claims 1-18 are indefinite in the recitation of a "CD40 agonist" because the agonistic properties are not recited and "are ill-defined to apprise the ordinary artisan of the metes and bounds of the claimed invention." Without addressing the merits of the rejection, claims 1 and 9 have been amended and, as amended, no longer recite the term "CD40 agonist."

d) The Office alleges claims 11 and 12 are indefinite in reciting SEQ ID NOs because there was no sequence listing for the instant application and that the instant application is not in sequence compliance. In reply, claim 11 is newly amended and, as amended, does not recite any SEQ ID NOs. Claim 12 is newly canceled herein. Thus, in view of the amendments to claim 11, and the cancellation of claim 12, the rejection is believed to be overcome.

e) Applicants have identified support in the specification for the amendments to the claims.

The rejections under 35 U.S.C. § 112, second paragraph, are believed to be overcome in view of the amendments to the claims and arguments above. Reconsideration and withdrawal of the rejections is respectfully requested.

C. **Rejection of Claims 11, 12, 15 and 18 Under 35 U.S.C. § 112, First Paragraph**

Claims 11, 12, 15 and 18 are rejected under 35 U.S.C. § 112, first paragraph, for purportedly lacking enablement. The rejection is respectfully traversed. Claim 12 is newly cancelled.

The Office, at page 4 of the Office Action, alleges the S2C6 and rituximab antibodies are required to practice the claimed invention and, as required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. The Office has invited Applicants to deposit the appropriate cell lines or the anti-CD20 and anti-CD40 antibodies in order to overcome the alleged lack of enablement.

However, and as discussed above, the S2C6 antibody (anti-CD40) and the rituximab antibody (anti-CD20) are produced by cell lines (hybridomas and transfectomas) deposited with the ATCC®. These anti-CD20 and anti-CD40 antibodies, via the cell lines for producing the antibodies, are thus readily available to the public through the depository, as well as through commercial suppliers.

Anderson discloses the nucleotide and amino acid sequences for both the chimeric and non-chimeric anti-CD20 antibody in Figures 1-5. Therefore the sequences are readily available to the public. Siegall discloses the ATCC® deposit number of the hybridoma comprising the genes encoding the S2C6 anti-CD40 antibody. Siegall further discloses both recombinant and chemical synthetic methods that may be used to produce the genes encoding the anti-CD40 antibody using the DNA from the hybridoma (Siegall, column 9, line 10 through column 10, line 35, for example). Thus, one of skill is easily able to recombinantly produce, or have commercial suppliers produce, both the anti-CD20 and anti-CD40 antibodies.

Lastly, as the Office is aware, Applicants are not required to teach what is known in the art. The nucleotide sequences, amino acid sequences and methods for producing both the anti-CD20 and anti-CD40 antibodies are known in the art at least as evidenced by U.S. patent numbers 6,843,989 (Siegall et al., anti-CD40) and 5,736,137 (Anderson et al., anti-CD20). Thus, even if, and only for the sake of argument, the cell line deposits lost viability, one of skill, having both the nucleotide and amino acid sequences, could continue to produce the anti-CD20 and anti-CD40 antibodies necessary to practice the claimed invention.

The Office, at page 5 of the Office Action, argues that Applicant did not make of record whether the requirements for the deposit of biological materials were satisfied. However, whether the requirements for the deposit of biological materials were satisfied is believed to be immaterial because the public availability of both the nucleotide and amino acid sequences of the antibodies permits one of skill to make, or acquire, the antibodies.

There are many factors that may be used as indicia that a biological material is known and readily available to the public. Relevant factors include commercial availability, references to the biological material in printed publications, declarations of accessibility by those working in the field, evidence of predictable isolation techniques, or an existing deposit made in accordance with these rules. Each factor alone may or may not be sufficient to demonstrate that the biological material is known and readily available.

Regarding Office arguments as to the commercial availability of the antibodies, the concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient. The term "readily" used in the phrase "known and readily available" is

considered appropriate to define that degree of availability which would be reasonable under the circumstances. Unless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent, current availability would satisfy the requirement. The incentives provided by the patent system should not be constrained by the mere possibility that a disclosure that was once enabling would become non-enabling over a period of time through no fault of the patentee. *In re Metcalfe*, 410 F.2d 1378, 161 USPQ 789 (CCPA 1969). See, MPEP § 2404.01.

In view of the amendments to the claims to now recite ATCC® deposit accession numbers and in view of the arguments, above, Applicants have sufficiently demonstrated the antibodies are known and readily available to the public. Reconsideration and withdrawal of the rejection is respectfully requested.

D. Objection to Specification Under 35 U.S.C. § 132

The Examiner objected to the specification under 35 U.S.C. § 132 for purportedly introducing new matter into the disclosure of the invention. The objection is respectfully traversed.

The Office alleges the amendment filed 2/28/06 introduces new matter into the disclosure. Allegedly, the added material not supported by the specification is SEQ ID NO: 1 and SEQ ID NO2 , SEQ ID NO:6 and SEQ ID NO: 7 of WO 00/75348 on page 20.

Without addressing the propriety of the objection, or the assertion of "new matter," the material added by way of amendment to the claims is canceled herein. It is believed the objection should be withdrawn and such is respectfully requested.

E. Rejection of Claims 11-12 Under 35 U.S.C. § 112, First Paragraph

Claims 11-12 are rejected under 35 U.S.C. § 112, first paragraph, for purportedly lacking enablement. The rejection is respectfully traversed. Claim 11 is newly amended. Claim 12 is newly canceled.

The Office alleges the specification as originally filed does not provide support for the invention as claimed in the previous Amendment (*i.e.*, "S2C6 comprises VL amino acid sequences of SEQ ID NO:1 and SEQ ID No: 2 and VH amino acid sequences

of SEQ ID NO: 6 and SEQ ID NO: 7 of WO 00/75348."). However, the subject matter has been cancelled from claim 11. Claim 12 has been cancelled in its entirety.

Further arguments at pages 5-7 of the Office Action concerning incorporation by reference are moot in view of the cancellation of the subject matter from the specification (See, amendments to the specification, above) and claims.

In view of the cancellation of claim 12 and the amendments to claim 11, it is believed the rejection has been overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

F. Rejection of Claims 1-18 and 31 Under 35 U.S.C. § 112, First Paragraph

Claims 1-18 and 31 are rejected under 35 U.S.C. § 112, first paragraph, for purportedly containing new matter and written description. The rejection is respectfully traversed. Claims 12 and 31 are newly cancelled herein; thus the rejection of claims 12 and 31 is moot.

The Office, at pages 7-8 of the Office Action, alleges the specification as filed does not provide support for the phrase "CD40 agonist." Without addressing the propriety of the rejection, the phrase "CD40 agonist" has been deleted from claims 1 and 9.

The amendments to claims 1 and 9 are believed to overcome the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

G. Rejection of Claims 1-18 Under 35 U.S.C. § 102(e)

Claims 1-18 are rejected under 35 U.S.C. § 102(e), as being anticipated by Hanna et al. (U.S. 2001/0018041 A1) [Hanna] in view of Armitage et al. (U.S. 5,674,492) [Armitage] (as cited in paragraphs [0013] and [0104] of Hanna) , in view of specification page 2, paragraph [0001], and in view of Fanslow et al. (U.S. 2005/0129689 A1) paragraphs [0005] and [0036] [Fanslow]. The rejection is respectfully traversed. Claims 1, 9, 11, 15 and 18 are newly amended. Claim 12 is newly cancelled; thus, the rejection of claim 12 is moot.

The Office arguments spanning pages 8-10 are briefly summarized as follows:

The teachings of agonistic anti-CD40 antibodies are acknowledged by page 2, paragraph 1 of the instant application and paragraphs [0005] and [0036] of Fanslow. Paragraphs [0013] and [0104] of Hanna contemplate the anti-CD40 antibodies taught by Armitage. Armitage teaches agonistic anti-CD40 antibodies such as the M2 and M3 antibodies.

Based on the foregoing, the Office concludes Hanna (referencing Fanslow and Armitage) teaches the use of agonistic anti-CD40 antibodies, including its combination with anti-CD20 antibodies, in the treatment of B cell lymphoma and leukemia.

Contrary to the position of the Office, Hanna (whether with or without Fanslow and Armitage, together or alone) does not anticipate claims 1-18. As the Office is aware, a reference must teach each and every element as set forth in the claim in order to anticipate. ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). In the instant case, claim 1 is newly amended to recite that it is the combination of anti-CD20 agents and anti-CD40 agents which is sufficient for the treatment of neoplastic disease or disorders. Claim 1 has been rewritten to more clearly claim the invention, *i.e.*, that it is the combination of anti-CD20 and anti-CD40 agents which is sufficient to provide a therapeutic effect.

Claim 1, as amended, differs from Hanna in at least two aspects: claim 1 requires a combination of anti-CD20 and anti-CD40 agents; and, claim 1 requires the combination to be sufficient for effective therapeutic treatment.

HANNA FAILS TO TEACH THE COMBINATION OF ANTI-CD20 AND ANTI-CD40 ANTIBODIES

Hanna is directed to, *inter alia*, administering a therapeutically effective amount of an antibody or antibody fragment (i.e., anti-CD40 agent) which binds to CD40L ([0017]), in combination with one or more other agents. "CD40L," as designated by

Hanna, is the ligand binding to CD40. Thus, Hanna teaches, *inter alia*, administration of an antibody to the ligand binding to CD40.

Another object of Hanna's invention is to provide a combination therapy for the treatment of a B-cell lymphoma or a B-cell leukemia comprising an anti-CD40L antibody or antibody fragment or CD40L antagonist and at least one of the following (a) a chemotherapeutic agent or a combination of chemotherapeutic agents, (b) radiotherapy, (c) an anti-CD20 antibody or fragment thereof and (d) an anti-CD40 antibody or fragment thereof ([0018]). Hanna discloses treatment using anti-CD40L antibodies alone or in conjunction with anti-CD20 antibodies ([0092]). Hanna thus focuses on the use of anti-CD40L antibodies and antagonists (see, for example, ¶s [0018], [0037], and [0059]) to produce the claimed effect and Hanna's composition must always comprise at least the antiCD40L antibody. Hanna does not disclose, and does not contemplate, treatment using a combination of anti-CD20 and anti-CD40 agents as is claimed in currently amended claim 1.

As the Office is aware, "An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the art." *ATD Corp. V. Lycall, Inc.*, 159 534, 48 USPQ2s 1321 (Fed. Cir. 1998). And, "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed; where there are differences between the reference disclosures and the claim, a rejection must be based on obviousness under Section 103." *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Because Hanna's invention is focused on treatment using an anti-CD40L antibody (or fragments thereof or antagonists thereto) and at least one other agent, and because Hanna does not teach a treatment using a combination of anti-CD20 and anti-CD40 agents, Hanna does not teach each and every element of claim 1.

HANNA FAILS TO TEACH THE SUFFICIENCY OF THE ANTI-CD20/ANTI-CD40 ANTIBODY COMBINATION FOR EFFECTIVE THERAPEUTIC TREATMENT

Hanna does not teach the anti-CD20/anti-CD40 agent combination of claim 1. Because Hanna fails to teach the anti-CD40 and anti-CD20 antibody combination, Hanna necessarily fails to teach an anti-CD40 and anti-CD20 antibody combination that is sufficient for treatment of disease or has therapeutic efficacy.

Hanna's therapeutic treatment requires the use of antiCD40L antibodies and antagonists (see, for example, ¶ [0100]) alone or in combination with one or more other agents. For relapsed or resistant Hodgkins Disease (HD), Hanna discloses conventional dose salvage combination regimens (see, for example, ¶ [0092] teaching the use of VABCD: vincoblastine, doxorubicin, dacarbazine, lomustine and bleomycin) in combination with antiCD40L antibodies, alone or in conjunction with anti-CD20 antibodies ([0100]). See, for example, ¶ [0096] and ¶ [0097] teaching use of radiotherapy and other forms of chemotherapy in conjunction with use of the anti-CD40L antibodies or anti-CD40L antagonists.

At pages 9-10 of the Office Action, the Office discusses the teachings of Armitage and Fanslow with respect to the M2 and M3 antibodies, which are agonistic anti-CD40 antibodies. However, the arguments are not relevant to Applicants' claimed invention which is a combination of anti-CD40 and anti-CD20 agents wherein the combination is sufficient for therapeutically effective treatment of neoplastic diseases or disorders. No claim currently recites the term "agonistic."

Further, the Office has used an improper legal standard ("On this record, it is reasonable to conclude...") (emphasis added) in the determination that claims 1-18 and 31 should be rejected under 35 U.S.C. § 102(e). As the Office is aware, a reference anticipates only if the reference teaches each and every element of the claim.

Because Hanna fails to teach a combination of anti-CD40 and anti-CD20 antibodies and that the combination is sufficient for therapeutically effective treatment of neoplastic disease or disorders, Hanna cannot anticipate claim 1, or, claims 2-11 and 13-18 dependent therefrom. In view of the deficiencies of Hanna, and the use of an improper legal standard, the rejection of claims 1-11 and 13-18 under 35 U.S.C. § 102(e) is legally improper. Reconsideration and withdrawal of the rejection is respectfully requested.

H. Rejection of Claims 1-18 and 31 Under 35 U.S.C. § 103(a)

Claims 1-18 and 31 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Hanna et al. (U.S. 2001/0018041 A1) [Hanna] in view of Siegall et al. (U.S. 6,843,989) [Siegall] and Grillo-Lopez (U.S. Patent No. 6,455,043) [Grillo-Lopez] and further in view of Armitage et al. (U.S. 5,674,492) [Armitage] (as cited in paragraphs [0013] and [0104] of Hanna), and Benoit et al. (Immunopharmacology 35: 129-139, 1996) [Benoit] and further in view of paragraphs [0005] and [0036] of Fanslow et al. (U.S. 2005/0129689 A1) [Fanslow]. Claims 1, 9, 11, 15 and 18 are newly amended. Claims 12 and 31 are newly canceled; thus, the rejection of claims 12 and 31 is moot. The rejection is respectfully traversed.

Applicants' comments set forth above regarding the failings of Hanna are pertinent and incorporated herein in their entirety. Briefly, Hanna fails to teach or suggest a combination of anti-CD40 and anti-CD20 antibodies and that the combination is sufficient for therapeutically effective treatment of neoplastic disease or disorders. Further, none of the other cited prior art references cure the deficiencies of Hanna, as discussed below.

Siegall is cited by the Office, *inter alia*, for teaching the treatment of cancer, leukemias, lymphomas, solid tumors and multiple myelomas with CD40 specific antibodies, including the S2C6 CD40 specific antibodies of the instant invention. Office Action at 11.

Grillo-Lopez is cited by the Office, *inter alia*, for teaching the treatment of various tumors with CD20 antibodies and teaching the expression of CD20 on multiple myelomas in addition to leukemias and lymphomas. Office Action at 12.

Armitage is cited by the Office, *inter alia*, for teaching the M2 and M3 agonistic anti-CD40 antibodies. Office Action at 9.

Fanslow is cited by the Office, *inter alia*, for teaching the M2 and M3 antibodies, which are agonistic anti-CD40 antibodies, as those antibodies that mimic the biological effects of CD40L and that are useful in the treatment of disease characterized by neoplastic diseases expressing CD40 such as B lymphomas, melanomas and carcinomas. Office Action at 9.

Benoit is cited by the Office, *inter alia*, for teaching the increased inhibition of proliferation of B cell lymphomas following ligation of CD40 and CD20. Office Action at 11.

The Office concludes "Given both the therapeutic use of CD40 specific antibodies and CD20 specific antibodies to treat various neoplastic diseases, including leukemias and lymphomas, myelomas and solid tumors, the ordinary artisan would have been motivated to combine the two antibody specificities as taught by Hanna in combination therapies to target other neoplastic tissues in order to increase the efficacy of cancer treatment." Office Action at 12. The Office is incorrect in both the assessment of the teachings of Hanna, and in the assessment of the motivation to combine one or more of Siegall, Grillo-Lopez, Fanslow, Armitage and Benoit with Hanna.

As discussed above, Hanna is silent on a combination of anti-CD40 and anti-CD20 antibodies which is sufficient for therapeutically effective treatment of neoplastic diseases or disorders as is claimed in newly amended claim 1. However, none of Siegall, Grillo-Lopez, Fanslow, Armitage or Benoit, alone or in any combination, cure the deficiencies of Hanna.

Siegall, teaching anti-CD40 antibodies, does not teach or suggest a combination of anti-CD40/antiCD20 antibodies. Further, a computer word search of the Siegall patent discloses only two mentions of the term "CD20": the first is in the title of reference and second occurrence is in the section entitled "7.1.3 Peripheral Blood B Cell Isolation," where in it is disclosed that "Peripheral blood B cells were isolated by positive selection using immobilized antibodies against both CD19 and CD20." Siegall, silent on CD20 antibodies except for their use to obtain an isolated B cell population, cannot suggest a CD20/CD40 antibody combination which is sufficient for therapeutically effective treatment of neoplastic diseases or disorders.

Grillo-Lopez, teaching anti-CD20 antibodies, does not teach or suggest a combination of anti-CD20 antibodies with anti-CD40 antibodies. In fact, Grillo-Lopez does not mention and does not contemplate use of CD20 antibodies in conjunction with any other antibodies in therapeutic treatments. See, for example, column 2, lines 4-8, wherein it is disclosed "In particular, it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy or chemotherapy." In addition, a computer word search of the Grillo-Lopez patent for the term "CD40" did not find any occurrences of the term. Because Grillo-Lopez is silent on CD40 antibodies, Grillo-Lopez does not mention, and therefore cannot suggest, a CD20/CD40 antibody combination, let alone a combination which is sufficient for therapeutically effective treatment of neoplastic diseases or disorders.

Armitage teaches, *inter alia,* independent administration of anti-CD40 antibodies and anti-CD20 antibodies to determine the effect of the antibodies on tumors in SCID mice. See, for example, Example 5. However, Armitage failed to administer a combination of anti-CD20 and anti-CD40 antibodies, despite administering each one separately, testing the effects of each antibody separately, and determining that each antibody alone had an inhibitory effect on the occurrence of the lymphoma (See, Table 2). Thus, the combination of anti-CD20 and anti-CD40 antibodies together is not an

obvious combination because Armitage, using each antibody separately in multiple separate experiments (See, for example, Table 2 and Table 3), failed to use, and doesn't suggest using, the combination.

Fanslow teaches, *inter alia*, the use of anti-CD40 antibodies in conjunction with phototherapy and is silent on anti-CD20 antibodies.

Benoit teaches, *inter alia*, ligation (cross-linking) of several surface molecules including CD19, CD20, and CD95 in combination with CD40 for growth inhibition of tumor cells. Benoit describes experiments to test the growth inhibitory effects of anti-CD20 antibody and anti-CD40 antibody on various NHL cell lines when the antibodies have been cross-linked using goat anti-mouse Ig (GAM). The results are presented in Table 2, page 132, as percentage inhibition relative to control. For example, exposure of Raji cells to cross-linked anti-CD20 and to cross-linked anti-CD40 antibodies results in 33% inhibition of growth, while the inhibition using cross-linked anti-CD20 antibody alone or cross-linked anti-CD40 antibody alone is 62% and 113% respectively (Page 132, Table 2, and, footnote "c").

Therefore, the results of Benoit are based on an experimental protocol involving use of an antibody which cross-links both anti-CD20 and anti-CD40 antibodies. Claim 1 is clearly directed, *inter alia*, to a combination of a CD40 specific binding agent and a CD20 specific binding agent, wherein said combination is sufficient for therapeutically effective treatment. The claimed combination does not require cross-linking agents or GAM.

Benoit does not appreciate or recognize that a combination of anti-CD20/anti-CD40 antibodies alone is sufficient for therapeutically effective treatment. In fact, Benoit is specifically interested in determining if a combination of other signals, such as cross-linking of several surface molecules, cAMP and butyrate, with the CD40-mediated signal were additive at inhibiting NHL growth (see, Benoit, page 130, left column, last

paragraph). In every experiment, Benoit adds a cross-linking antibody. Benoit never contemplates a combination of anti-CD20/anti-CD40 antibodies alone.

Thus, one of skill, reading Benoit, would not be motivated by the results of Benoit to use a combination of anti-CD20/anti-CD40 antibodies without the cross-linking GAM because Benoit does not recognize any advantage or expected beneficial results of an anti-CD20/anti-CD40 antibody combination without the cross-linking antibody GAM.

As the Office is aware, there are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obviousness was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

FACT THAT REFERENCES CAN BE COMBINED OR MODIFIED IS NOT SUFFICIENT TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In the instant case, Hanna, teaching anti-CD40L antibodies or antagonists and their use in treatments, does not teach a CD20/CD40 antibody combination which is sufficient for therapeutically effective treatment of neoplastic diseases or disorders. None of Siegall, Grillo-Lopez,

Fanslow, or Armitage teaches or suggests the desirability of a CD20/CD40 antibody combination as discussed above. Benoit can be considered as teaching away from a anti-CD20/anti-CD40 antibody combination in view of the uniformly unfavorable experimental results obtained with the anti-CD20/anti-CD40 antibody combination.

Hanna provides no motivation to use an anti-CD20/anti-CD40 antibody combination alone without a CD40L antibody because Hanna does not suggest that such a combination would be sufficient for therapeutically effective treatment of neoplastic diseases or disorders. The availability in the art of references teaching anti-CD20 antibodies and others teaching anti-CD40 antibodies is insufficient motivation to combine them with Hanna's invention when no reference teaches or suggests the desirability of a CD20/CD40 antibody combination, let alone a CD20/CD40 antibody combination sufficient for therapeutically effective treatment of neoplastic diseases or disorders. This teaching was first provided by Applicant's specification. The Examiner is using the specification and hindsight to improperly make Applicant's claimed invention seem obvious.

FACT THAT THE CLAIMED INVENTION IS WITHIN THE CAPABILITIES OF ONE OF ORDINARY SKILL IN THE ART IS NOT SUFFICIENT BY ITSELF TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS

A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993); *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.).

The Office argues "[t]he strongest rationale for combining reference [sic] is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of

reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination." Office Action at 12. However, as discussed above, none of Hanna, Siegall, Lopez-Grillo, Armitage, Fanslow or Benoit provides any motivation for combination.

Hanna is directed to the use of antiCD40L antibodies or antagonists, alone or in combination with one or more other agents such as CD20, CD40 antibodies, soluble CD40 ligands and chemotherapeutic agents. To arrive at the method of claim 1 using Hanna as a reference (either primary or secondary), one of skill would have to rationalize why Hanna's use of the CD40L antibodies (and CD40L antagonists, etc.) can be eliminated, thus completely destroying Hanna's invention.

There is no recognition found in any of the references that some advantage or expected beneficial result would have been produced by the combination of references as suggested by the Office. No cited prior art reference, alone or in combination with any other reference, suggests the invention as claimed in newly amended, independent claim 1. Claim 1, and dependent claims 2-11 and 13-18, are patentable over the cited prior art of record.

In view of the amendments to the claims, and arguments above, the rejection is believed to be overcome. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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October 5, 2006
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(54) Title: RECOMBINANT ANTI-CD40 ANTIBODY AND USES THEREOF

(57) Abstract: The present invention relates to methods and compositions for the prevention and treatment of cancer, inflammatory diseases and disorders or deficiencies of the immune system. The methods of the invention comprise administering a CD40 binding protein that potentiates the binding of CD40 to CD40 ligand.